ORIGINAL INVESTIGATION

Psilocybin links binocular rivalry switch rate to attention and subjective arousal levels in humans

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Abstract

Rationale Binocular rivalry occurs when different images are simultaneously presented to each eye. During continual viewing of this stimulus, the observer will experience repeated switches between visual awareness of the two images. Previous studies have suggested that a slow rate of perceptual switching may be associated with clinical and drug-induced psychosis.

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Objectives The objective of the study was to explore the proposed relationship between binocular rivalry switch rate and subjective changes in psychological state associated with 5-HT$_{2A}$ receptor activation.
Materials and methods This study used psilocybin, the hallucinogen found naturally in *Psilocybe* mushrooms that had previously been found to induce psychosis-like symptoms via the 5-HT$_{2A}$ receptor. The effects of psilocybin (215 μg/kg) were considered alone and after pretreatment with the selective 5-HT$_{2A}$ antagonist ketanserin (50 mg) in ten healthy human subjects.
Results Psilocybin significantly reduced the rate of binocular rivalry switching and increased the proportion of transitional/mixed percept experience. Pretreatment with ketanserin blocked the majority of psilocybin's "positive" psychosis-like hallucinogenic symptoms. However, ketanserin had no influence on either the psilocybin-induced slowing of binocular rivalry or the drug's "negative-type symptoms" associated with reduced arousal and vigilance.
Conclusions Together, these findings link changes in binocular rivalry switching rate to subjective levels of arousal and attention. In addition, it suggests that psilocybin's effect on binocular rivalry is unlikely to be mediated by the 5-HT$_{2A}$ receptor.

Introduction

The search for the neural correlates of consciousness is becoming increasingly focused on visual illusions that can be used experimentally to manipulate conscious awareness. One of the most notable examples is binocular rivalry, a visual phenomenon that results when two different images are presented simultaneously to the left and right eye (Wheatstone 1838). Under these conditions, the observer

will experience repeated switches between awareness and suppression of the two "rivaling" images. For example, if vertical gratings are presented to one eye and horizontal gratings are presented to the other eye, the viewer will generally report seeing either only vertical or only horizontal gratings. Interestingly, one image will not dominate indefinitely, but the two images alternate their dominance every few seconds. Although the dominance is often complete, the transition between competing percepts can involve periods of mixed percept where a dynamic patchwork of horizontal and vertical gratings is perceived (for review, see Blake and Logothetis 2002; Tong et al. 2006).

To date, binocular rivalry has been used primarily as a tool to investigate the physiological processes underlying consciousness and the factors influencing perceptual grouping and awareness. However, there is increasing evidence that binocular rivalry may also reflect brain processes involved in determining more global aspects of conscious state. Changes in perceptual switch rate are now associated with clinical psychosis (Leonard et al. 2001; Miller et al. 2003; Pettigrew and Miller 1998), drug-induced altered states of consciousness (Carter et al. 2005b; Frecska et al. 2004), and meditation (Carter et al. 2005c). Previous rivalry studies have used functional imaging (Lee et al. 2005; Lumer et al. 1998; Tong and Engel 2001) and electrophysiological recording techniques (Leopold and Logothetis 1996; Sheinberg and Logothetis 1997) to identify neuronal activity that correlates with perceptual awareness. In contrast, this study employs a pharmacological approach to investigate the role of serotonin receptors in driving perceptual switches and the relationship between switch rate and an individual's psychological state.

Despite the growing evidence for an association between rivalry switching rate and subjective changes in conscious state, none of the current "mutual inhibition" models address this issue. These models generally propose that groups of neurons associated with the two rivalry percepts will directly suppress each other through mutual inhibitory connections. Over time, the dominant neurons will "fatigue", and their inhibitory effects will be reduced, resulting in a switch in perceptual dominance (Blake and Logothetis 2002; Wilson 2004; Wilson et al. 2001). Such models, which consider the influence of local neural interactions and some global variations in neurotransmitter levels, are able to account for a number of the psychophysical characteristics of binocular rivalry. They fail, however, to predict any clear association between switch rate and more global changes in conscious state. In contrast, one model that attempts to account for this link proposes that perceptual switches characteristic of all forms of rivalry are driven by large fluctuations in brainstem activity and associated neurotransmitter release (Pettigrew 2001). Spe-

cifically, this model suggests an integrated role for a number of brainstem nuclei encompassing regions such as the raphe nuclei, the ventral tegmental area, and the locus coeruleus, each of these nuclei being responsible for the respective release of serotonin (5-HT; Jacobs and Azmitia 1992), dopamine (Dahlstrom and Fuxe 1964), and noradrenalin (Foote et al. 1983). It is proposed that abnormal functioning of these brainstem nuclei may underlie symptoms of psychosis and disrupt the timing of oscillatory networks involved in binocular rivalry switching (Pettigrew 2001).

Psilocybin, the main psychoactive compound found in *Psilocybe* "magic" mushrooms, provides an opportunity to investigate this model from a pharmacological perspective because it is known to induce profound transient changes in conscious state. Psilocybin is known to alter sensory processing (Carter et al. 2004; Vollenweider et al. 2007), cognitive function (Carter et al. 2005a; Hasler et al. 2004; Wittmann et al. 2007), and to induce mystical-type experiences (Griffiths et al. 2006). Due to this capacity to drastically alter perceptual and cognitive processing, hallucinogens have proven to be a valuable tool with which to investigate the pharmacological mechanisms underlying different clinical symptoms in both human (Gouzoulis-Mayfrank et al. 1998; Umbricht et al. 2003; Vollenweider and Geyer 2001; Vollenweider et al. 1998) and animal models of psychosis (Beique et al. 2007; Gonzalez-Maeso et al. 2007; Lambe and Aghajanian 2007; Weisstaub et al. 2006).

Like other hallucinogens, anesthetics, and antipsychotic medications, the subjective effects of psilocybin are believed to result from its ability to functionally mimic endogenous neurotransmitters at specific receptor sites. Specifically, psilocin (4-hydroxy-N,N-dimethyltryptamine), the pharmacologically active metabolite of psilocybin, is believed to act primarily through the 5-HT$_{2A}$ receptor for which it shows high affinity (K_i=6 nM). Psilocin also shows some affinity for the 5-HT$_{1A}$ (K_i=49 nM; McKenna et al. 1990) and 5-HT$_{2C}$ receptors (Blair et al. 2000); however, the role of these receptors is still unclear (for review, see Nichols 2004). 5-HT$_{2A}$ receptors are located predominantly on the apical dendrites of pyramidal cells of the cortex (Jakab and Goldman-Rakic 1998), with activation of these receptors leading to increased cortical activity believed to be driven by glutamatergic excitatory postsynaptic potentials, particularly in layer V (Aghajanian and Marek 1997). This effect is most pronounced in the frontal cortex (Vollenweider et al. 1997) where there is an increased density of 5-HT$_{2A}$ receptors as compared to more posterior regions (Wong et al. 1987). In contrast, 5-HT$_{1A}$ receptors serve an inhibitory function and are highly expressed presynaptically in the raphe nucleus of the brainstem (Sotelo et al. 1990). Small concentrations of postsynaptic 5-HT$_{1A}$ receptors also have been identified in

the hippocampus (Hamon et al. 1990) and in prefrontal cortex (PFC; Pazos and Palacios 1985). The primary effect of 5-HT$_{1A}$ activation, however, is to reduce raphe cell firing rate and decreased 5-HT release from the terminal projection fields throughout the cortex (Aghajanian and Hailgler 1975; Sprouse and Aghajanian 1986).

On the basis of the known properties of psilocybin and the nature of the proposed brainstem oscillator described above, it was predicted that the inhibition of 5-HT release from the raphe nucleus, in combination with an increase in cortical activation induced by psilocybin, would reduce the relative influence of the brainstem nuclei and cause rivalry alternations to become slower and less regular. Confirming these predictions, psilocybin was found dose-dependently to reduce the rate of binocular rivalry switching in a manner reflecting the subjective changes in conscious state (Carter et al. 2005b). This result was consistent with the finding that the hallucinogenic N,N-dimethyltryptamine (DMT)-containing brew ayahuasca significantly slowed the rate of rivalry switches (Frecska et al. 2004), and an incidental observation that rhythmicity of binocular rivalry alternations was greatly increased 10 h after the reported consumption of lysergic acid diethylamide (Carter and Pettigrew 2003).

5-HT$_{2A}$ receptor activation has generally been considered to be the main factor contributing to the hallucinogenic properties of psilocybin (Nichols 2004; Vollenweider et al. 1998). Confirming this assumption, specific neural and signaling mechanisms proposed to be responsible for hallucinogenic effects were recently identified and linked to these cortical 5-HT$_{2A}$-receptor-regulated pathways (Gonzalez-Maeso et al. 2007). To determine whether the 5-HT$_{2A}$ receptor was similarly involved in psilocybin's effect on binocular rivalry, this study used pretreatment with the selective 5-HT$_{2A}$ antagonist ketanserin (K_i= 2.6 nM; Richelson and Souder 2000). Ketanserin prevents psilocybin activation of the 5-HT$_{2A}$ receptor and previously had been found to block the majority of psilocybin's hallucinogenic effects (Vollenweider et al. 1998). This study aimed to investigate whether psilocybin's slowing of binocular rivalry switching would be similarly blocked by ketanserin or if the changes in perceptual rhythms could be dissociated from the drug induced "psychosis-like" psychological changes.

The study involved ten healthy human subjects being tested under four drug conditions: placebo; psilocybin (215 μg/kg); ketanserin (50 mg); and psilocybin plus ketanserin. Binocular rivalry was induced by presenting vertical and horizontal gratings to the subject's left and right eye, respectively. Perceptual switching patterns were measured 45 min before and at 30, 60, 90, 135, 180, 240, 300, 360, and 420 min after psilocybin/placebo intake. The adjective mood rating scale (AMRS) and the altered states of consciousness rating scale (5D-ASC) were used to assess changes in subjective experience.

Materials and methods

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich, and the use of psilocybin was authorized by the Swiss Federal Office of Public Health, Bern.

Subjects and dosing

Ten healthy volunteers (six men, four women) aged 21 to 31 years (mean±SD=26.0±2.3) were recruited from the local university and technical college. All subjects had normal or corrected to normal vision and were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. They also were deemed by psychiatric interview to have no personal or family (first-degree relatives) history of major psychiatric disorders or evidence for alcohol or substance abuse. Five of the participants reported previous experience with psilocybin through the ingestion of *psilocybe* mushrooms; the other five were psilocybin-naïve. Subjects were reimbursed for their time and were free to withdraw from the study at any time.

The psilocybin (215 μg/kg), ketanserin (50 mg), and lactose placebo were administered in gelatine capsules of identical appearance. The 215-μg/kg dose of psilocybin was chosen because the subjective effects induced by this dose were previously shown to be effectively blocked by ketanserin pretreatment (Vollenweider et al. 1998) and because it was intermediate between the two doses of psilocybin used in the original binocular rivalry study (Carter et al. 2005b). In contrast to the 40-mg dose of ketanserin used by Vollenweider et al. (1998), 50 mg of ketanserin was chosen for the current study because 40 mg of ketanserin was found to cause significant, but not total, blockade of psilocybin's effects. It was anticipated that a slightly higher dose might result in a more complete reduction of subjective effects.

Psilocybin was obtained through the Swiss Federal Office of Public Health. Capsules of psilocybin (1 and 5 mg) and ketanserin (50 mg) were prepared at the pharmacy of the Cantonal Hospital of Aarau, Switzerland, and quality was assured by tests for identity, purity, and uniformity of content.

Binocular rivalry

Stationary green vertical and horizontal gratings were presented to the subject's left and right eye, respectively,

using liquid crystal goggles. Viewed from a distance of 60 cm, the gratings had a duty cycle of 0.33 (one third green two thirds black) and a spatial frequency of 1.5 cycles/degree of visual angle. The entire rivalry patch was presented as a disc that subtended 4° of visual angle. These stimulus parameters were chosen for maximum clarity and reportability for naïve subjects and are the same as those described in Carter et al. (2005b).

Responses were recorded on a keyboard with two raised buttons, one with a ridge aligned perpendicular to the observer (vertical) and the other running from left to right (horizontal). Subjects were instructed to focus only on the orientation of the gratings and report their respective predominance by pushing the appropriate button. If a mixed percept of the two orientations was experienced, either as a grid or a patchwork combination of the two gratings, they were instructed to press a third flat button. In contrast to the previous binocular rivalry study (Carter et al. 2005b), subjects were instructed to report any period of mixed percept. This included prolonged periods of transition between the exclusive dominance of either of the respective percepts. Data were collected in a single block consisting of 4×60-s trials, with a 30-s break between each trial.

Before each binocular rivalry session, subjects were presented with a 1-min movie of simulated rivalry to ensure that subjects were capable of reporting their visual experiences accurately during drug-altered states. This "catch trial movie" consisted of the sequential presentation of vertical or horizontal gratings to both eyes. The grating images, identical to those used during the binocular rivalry condition, were generated using Matlab Psychtoolbox (Brainard 1997) and presented for durations of 0.5 to 5 s (selected at random using a uniform sampling distribution). During the presentation, subjects were given the same viewing and reporting instructions as those outlined for binocular rivalry. This allowed us to obtain information regarding response time and accuracy of response. Despite using the identical instructions for the catch trial movie as those used for the test period, it should be noted that the catch trial movie showed clean switches between vertical and horizontal gratings and did not include transition periods depicting a mixed state. Four different versions of the catch trial movie sequence were used in a randomized order.

Psychological ratings

The German version of the AMRS (Janke and Debus 1978) and the altered state of consciousness (5D-ASC) rating scale (Dittrich 1998) were used to assess the subjective effects under placebo and psilocybin, in line with previous studies (Hasler et al. 2004; Vollenweider et al. 1997).

The AMRS consists of 60 adjectives representing different mood states. Subjects were instructed to rate the extent to which each adjective was applicable to their current mood as: "not at all", "a little", "quite" and "strongly". The associated scores were then grouped into seven main factors (representative mode states shown in italics). (1) Performance-related activity (PRA); *efficient, active, concentrated*. (2) General inactivity (GI); *lethargic, tired, dazed*. (3) Extroversion (EX); *extroversion plus inverted scores for introversion*. (4) General positive mood (GPM); *self-confidence, heightened mood*. (5) Emotional excitability (EE); *excitability, sensitivity, aggressiveness*. (6) Anxiety–depressiveness (AD). (7) Dreaminess (DR).

The 5D-ASC is a visual analogue scale that measures alterations in waking consciousness associated with mood, perception, experience of oneself and of the environment, and cognitive processing. The 5D-ASC consists of 94 individual statements such as "I heard tones and noises without knowing where they came from." Subjects were required to mark their current state along a 100-mm line between "No, not more than usual" or "Yes very much more than usual." Each of the 94 items was given a score from 0 to 100, reflecting the distance (mm) from the end indicating no change. The items and their associated scores were then grouped to yield the following five main factors. (1) "Oceanic boundlessness" (OB), measures derealization and depersonalization accompanied with changes in affect ranging from heightened mood to mania-like euphoria and alterations in the sense of time. (2) "Anxious ego dissolution" (AED) measures ego-disintegration associated with loss of self-control, disordered thought, arousal, and anxiety. (3) "Visionary restructuralization" (VR) includes visual (pseudo-) hallucinations, synesthesia, changed meaning of percepts, facilitated recollection and imagination. (4) "Auditory alterations" (AA) refers to acoustic hallucinations and distortions in auditory experiences. (5) "Reduction of vigilance" (RV) relates to states of drowsiness, reduced alertness and impaired cognitive and attentional function.

Experimental design

The study was double-blind, and the order of dose assignment was counter-balanced. For each of the four experiment days (separated by at least 14 days), subjects were instructed to have a light breakfast before arrival at the hospital. Before testing began, blood pressure and heart rate were measured and subsequently monitored at hourly intervals throughout the day. After baseline "pretesting" of binocular rivalry, the ketanserin/placebo capsules were administered. Peak plasma levels of ketanserin are generally reached within 0.5 to 2 h (Perrson et al. 1991). Therefore, to ensure occupancy of the 5-HT$_{2A}$ receptor, the

psilocybin/placebo capsules were not administered until 90 min after the ketanserin.

Binocular rivalry was measured 45 min before and at 30, 60, 90, 135, 180, 240, 300, 360, and 420 min after psilocybin intake. Because plasma levels of psilocin, the active metabolite of psilocybin, peak approximately 105 ± 37 min after drug intake (Hasler et al. 1997), the AMRS was administered at pretest and again just before the 90-min binocular rivalry testing. After the 180-min measure of binocular rivalry, subjects were given the 5D-ASC rating scale and instructed to rate their experience retrospectively since drug intake (0–180 min).

At pretest and 120 min post-administration, subjects were additionally tested on attentional tracking and spatial working memory measures. The results from those experiments have been published elsewhere (Carter et al. 2005a). Subjects finished participation in the study approximately 7 h after psilocybin administration and were examined by the principal investigator before being released.

Results

Binocular rivalry

Mean phase duration was calculated as the average duration of time (s) that the subject reported uninterrupted dominance of the respective target. Using a repeated measures analysis of variance (ANOVA), significance was found for the main effects of drug $[F_{(3,27)}=6.87; p<0.01]$ and time $[F_{(10,90)}=11.71; p<0.001$; Fig. 1a]. Subsequent post hoc analysis revealed that psilocybin alone and after pretreatment with ketanserin led to significant increases in phase duration after psilocybin at 60, 90, and 135 min ($p<0.001$). At 180 min, only the psilocybin alone condition remained significantly greater than placebo ($p<0.001$). At no time point was a significant difference observed between the psilocybin alone and psilocybin plus ketanserin conditions. Similarly, no significant differences were seen between the placebo and ketanserin alone conditions. No effect of time/ repeated-testing was observed within either the placebo or ketanserin condition.

With respect to the amount of "mixed" percept reported, there was a significant main effect of time $[F_{(10,90)}=5.24; p<0.001]$ and time by dose interaction $[F_{(30,270)}=1.97; p<0.01]$. Post hoc analysis revealed that psilocybin increased the proportion of mixed percept at 90 and 240 min ($p<0.01$). Psilocybin plus pretreatment with ketanserin led to a significant increase at 135 min ($p<0.05$; Fig. 1b).

Key press responses to the catch-trial movie were assessed with respect to response accuracy (total number of incorrect responses) and response time for each individual. Response accuracy was not affected by drug
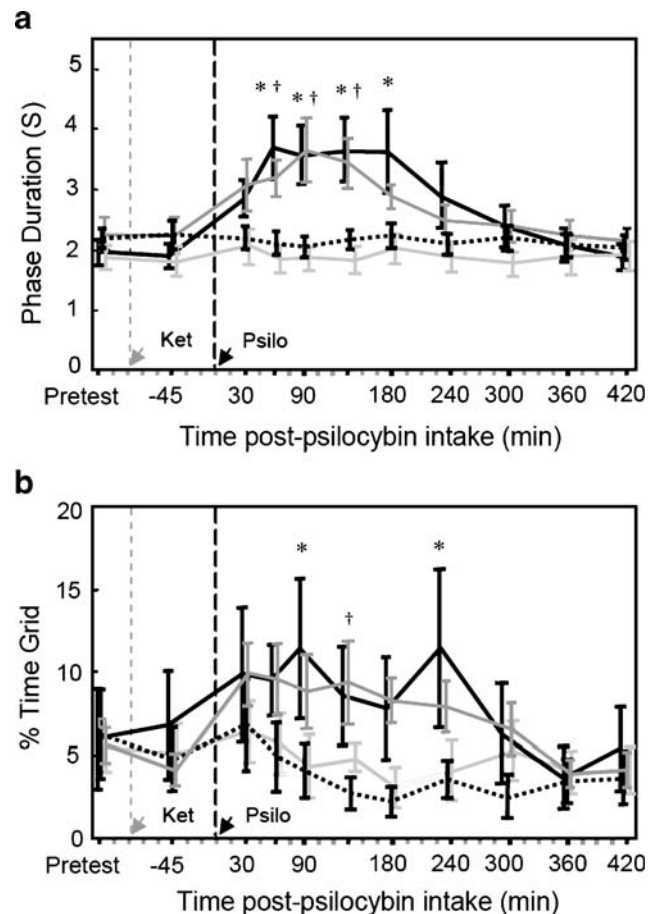

Fig. 1 Drug-induced changes in binocular rivalry for placebo (*dashed line*), psilocybin (*black*), psilocybin plus ketanserin (*dark gray*), and ketanserin alone (*light gray*). **a** Mean phase duration (time between perceptual switches) was significantly prolonged by psilocybin, and this effect was not reduced by pretreatment with ketanserin. There was no significant difference between placebo and ketanserin alone. **b** Similarly, both psilocybin alone and after pretreatment with ketanserin led to significant increases in the proportion of mixed percept grid/ patchwork. Significant difference ($p<0.05$) from placebo is denoted by '*' for psilocybin and '†' for psilocybin plus ketanserin. Error bars represent standard errors of the means

$[F_{(3,27)}=0.07; p=0.98]$ or testing time $[F_{(10,90)}=0.40; p=0.95$; Fig. 2a]. Response times did show a significant main effect of drug $[F_{(3,27)}=3.73; p<0.05]$ and time $[F_{(10,90)}=5.85; p<0.0001$; Fig. 2b]. However, the response times under psilocybin were significantly slower compared to placebo only at the 60-min time point ($p<0.01$). The combination of psilocybin and ketanserin led to slower response times at 60, 90, 180, and 300 min ($p<0.01$). There was no significant difference between placebo and ketanserin alone at any time point, nor was any difference found between time points within the placebo condition.

Psychological effects

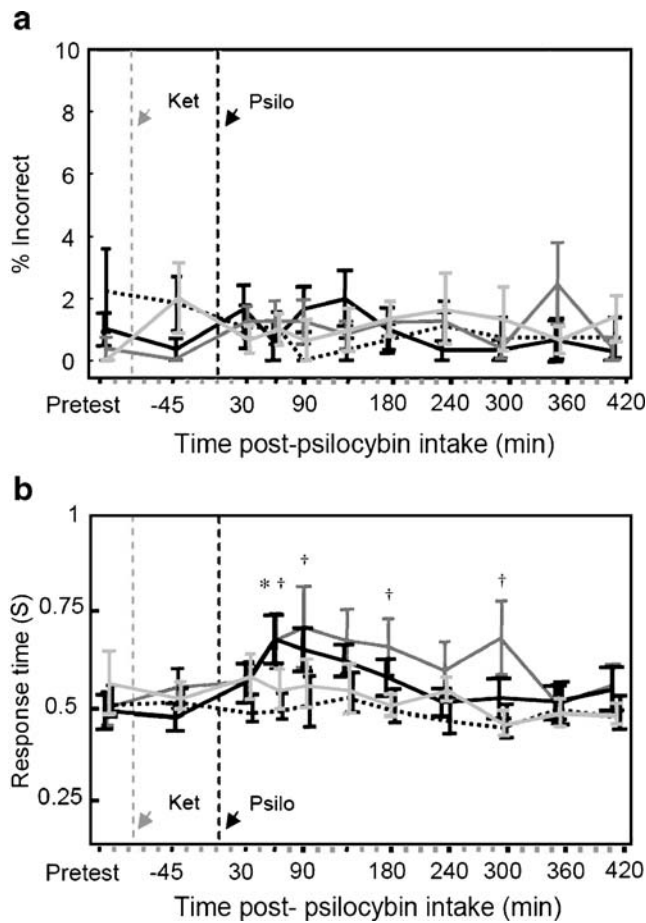The subjective effects of the four drug conditions, as measured by the AMRS and the 5D-ASC, are illustrated in

Fig. 2 Rivalry pretest catch-trial responses for placebo (*dashed line*), psilocybin (*black*), psilocybin plus ketanserin (*dark gray*) and ketanserin alone (*light gray*). **a** Response accuracy was not significantly affected by either of the four drug conditions. **b** However, mean response time was increased by psilocybin alone and after ketanserin pretreatment at a few time points. Significant difference ($p<0.01$) from placebo is denoted by '*' for psilocybin and '†' for psilocybin plus ketanserin. Error bars represent standard errors of the means

Fig. 3 Subjective effects experienced during placebo (*white*), psilocybin (*black*), psilocybin with ketanserin (*black/gray stripes*), and ketanserin alone (*gray*). **a** Change in scores for the AMRS from pretesting for the seven main factors: performance-related activity, general inactivity, extroversion, general positive mood, emotional excitability, anxiety–depressiveness, and dreaminess. **b** Results from the ASC questionnaire shown as the percentage of the total possible score for each of the five main factors: oceanic boundlessness, anxious ego dissolution, visionary restructuralization, auditory alterations, and reduced vigilance. Psilocybin caused significant changes, compared to placebo, in all factors except for auditory alterations. After pretreatment with ketanserin, the subjective effects of psilocybin were largely blocked, with only reduced vigilance remaining significantly elevated above placebo. The scores for placebo are not represented because they remained at zero for all five factors (signifying no change relative to normal). **c** The degree to which psilocybin slowed down the binocular rivalry phase duration was significantly correlated with the reduction in vigilance. The individual data points represent the corresponding changes, relative to placebo, for all ten participants. **d** The same positive relationship was seen for the effect of psilocybin plus ketanserin, relative to placebo, although this correlation was not significant. Significant difference ($p<0.05$) from placebo is denoted by '*' for psilocybin and '†' for psilocybin plus ketanserin, while differences between psilocybin alone and after ketanserin pretreatment are signaled by '‡'. The error bars represent standard errors of the means

Fig. 3a and b, respectively. To assess the influence of drug condition on the AMRS, difference scores were calculated by subtracting pretest values from the 90-min values for the seven main factors corresponding to: PRA, GI, EX, GPM, EX, AD, and DR. Using these difference scores, significant main effects were found for drug [$F_{(3,27)}=10.28$; $p<0.001$] and factor [$F_{(6,54)}=11.85$; $p<0.001$]. Tukey's post hoc analysis revealed that compared to placebo, psilocybin caused a significant increase in only one of the seven factors, DR ($p<0.0001$). After pretreatment with ketanserin, however, three factors showed significant changes (PRA: $p<0.01$; GI: $p<0.0001$; DR: $p<0.0001$). Comparing the psilocybin alone condition with the psilocybin after ketanserin pre-treatment condition, no significant differences were observed for PRA, EX, EE, AD, and DR; however, significant differences were seen for two factors (GI: $p<0.05$; GPM: $p<0.05$). There was no difference
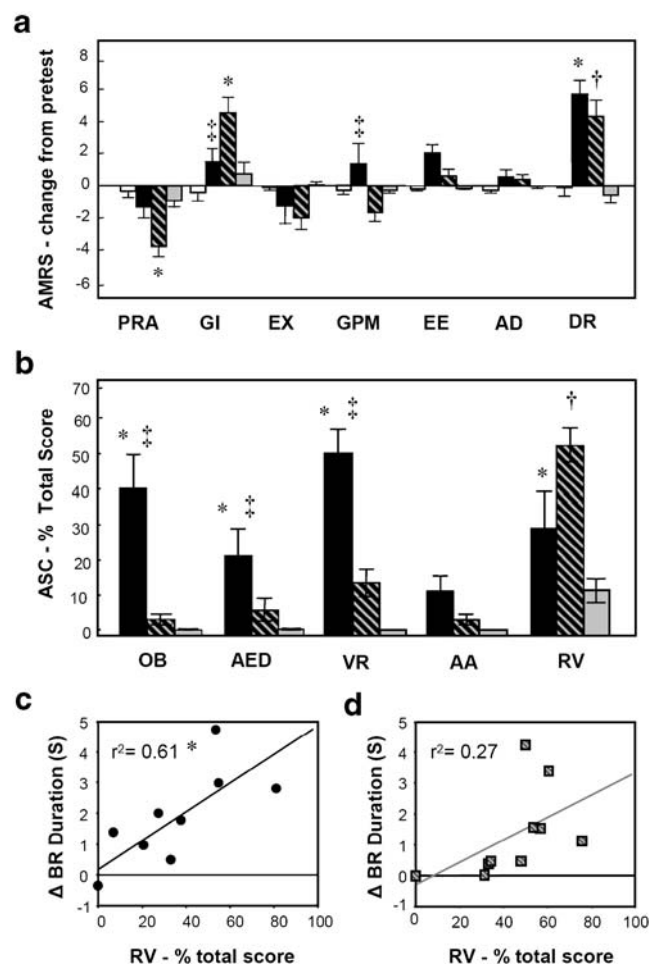
between placebo and ketanserin alone for any of the seven factors.

Scores for the 5D-ASC rating scale correspond to the five major factors: OB, AED, VR, AA, and RV. Using a repeated measures ANOVA, significant main effects were found for drug [$F_{(3,21)}=18.15$; $p<0.001$] and factor [$F_{(4,28)}=11.22$; $p<0.001$]. Tukey's post hoc analysis revealed that compared to placebo, psilocybin caused a significant increase in four of the factors (OB: $p<0.001$; AED: $p<0.001$; VR: $p<0.001$; RV: $p<0.05$). After pretreatment with ketanserin, the subjective effects of psilocybin were largely blocked with only RV remaining significantly effected ($p<0.001$). Comparing the psilocybin alone condition with the psilocybin after ketanserin pretreatment condition, no significant differences were observed for RV or AA; however, significant differences were seen for the other three factors (OB: $p<0.001$; AED: $p<0.05$; VR: $p<0.001$). Ketanserin alone caused no significant subjective effects. Please note that some of the results from the 5D-ASC rating scale described here, and illustrated in Fig. 3b, were reported in a previous publication describing measures of attentional tracking and spatial working memory performance that were taken during the course of the current experimental session (Carter et al. 2005a).

One key finding from these results is that ketanserin pretreatment was unable to block either psilocybin's slowing of binocular rivalry or the psychological effect pertaining to reduced arousal and vigilance. While these results are suggestive of a relationship between rivalry rate and levels of arousal/attention, it is not clear if this trend can also be seen at the level of individual subjects. To investigate this question, we plotted increases in binocular rivalry phase duration (relative to placebo at the 90 min time point) against changes in RV score from the 5D-ASC rating scale. Figure 3c shows that binocular rivalry slowed down the most in individuals that reported the greatest reduction in vigilance ($r^2=0.61$, $p<0.05$, $df=8$) in the psilocybin alone condition. A similar relationship was seen in the psilocybin plus ketanserin condition (Fig. 3d); however, this effect did not reach significance ($r^2=0.27$).

Discussion

The main findings of this study were that "hallucinogenic" levels of the mixed 5-HT$_{1A/2A}$ agonist psilocybin significantly slowed the rate of perceptual switching and increased the proportion of time experiencing the mixed/transitional percept during binocular rivalry. Neither of these effects was reduced by pretreatment with the 5-HT$_{2A}$ antagonist ketanserin despite the fact that ketanserin pretreatment blocked the majority of psilocybin's subjective psychological effects. The lack of difference between rivalry rate for the psilocybin alone and ketanserin pretreatment conditions indicates that the slowing of the rivalry is unlikely to be mediated by the 5-HT$_{2A}$ receptor population involved in psilocybin's subjective effects.

The apparent lack of involvement of the 5-HT$_{2A}$ receptor was contrary to our expectations, as it stood in contrast to current opinion (for review, see Nichols 2004) and recent evidence suggesting that indole hallucinogens such as psilocybin primarily act through the 5-HT$_{2A}$ receptor (Gonzalez-Maeso et al. 2007). Psilocybin has greater affinity for the 5-HT$_{2A}$ receptor compared to the 5-HT$_{1A}$ receptor (McKenna et al. 1990), and the subjective effects of psilocybin were previously shown to be blocked by the 5-HT$_{2A}$ antagonist ketanserin (Vollenweider et al. 1998). Reconciliation of our results with this clear emphasis on the 5-HT$_{2A}$ receptor as the biological target for psilocybin appears to lie in a slight difference in the rating scale used in the current study. The version of the 5D-ASC rating scale used here included an additional two measures compared to the scale reported in the study by Vollenweider et al. (1998). Consistent with previous results, we found that ketanserin pretreatment blocked the influence of psilocybin on the three core dimensions: OB—relating to mania-like symptoms; AED—associated with general anxiety; and VR—a measure of visual distortions and hallucinations. However, RV—a dimension pertaining to reduced levels of vigilance and arousal that was added to the more recent version of the 5D-ASC—was unaffected by ketanserin pretreatment. This result was mirrored by those of the AMRS, which found that psilocybin after pretreatment with ketanserin was associated with a reduction in PRA and increases in reported levels of GI and DR. These selective effects on subjective reports of reduced vigilance, concentration, activity and increased dreaminess are consistent with objective psychophysical measures obtained from the same subjects, showing that psilocybin, both alone and after pretreatment with ketanserin, impaired attentional tracking performance (Carter et al. 2005a).

Taken together, these results suggest that it may be possible to separate the "positive" psychosis-like effects (i.e., delusion, manic grandiosity, synesthesia, visual distortions/ hallucinations, disturbed self-image) from the "negative" symptoms associated with apathy and a reduction in general levels of arousal and attention. Although there do not appear to be any significant effects of ketanserin alone, it is interesting that ketanserin appears to potentiate the effects of psilocybin in some of the psychological ratings (RV, PRA, GI). It is possible that a more sensitive measure of psychological effects and perceptual switch rate may have identified subtle differences between the two conditions. Therefore, it is possible that pretreatment with ketanserin may have exaggerated or

altered psilocybin's actions, either through its action on the 5-HT_{2A} receptor or other yet to be identified mechanisms. Similarly, because participants in the study were not given a urine screen on assessment days, it is impossible to rule out an involvement of other substances of abuse. However, given that the drug effects were seen consistently across all participants, it seems unlikely that the results reflect the undisclosed use of prescription or illicit substances by individual participants.

These results have some clear clinical implications. Previously, it has been reported that binocular rivalry switching rate is significantly altered in individuals with schizophrenia and bipolar disorder compared to healthy control populations (Leonard et al. 2001; Miller et al. 2003; Pettigrew and Miller 1998). Therefore, it was predicted that in addition to blocking all of the "psychosis-like" effects of psilocybin, ketanserin pretreatment would similarly block any psilocybin-induced changes to the binocular rivalry rate. The finding that ketanserin had no effect on rivalry rate went against expectations. In contrast, the results of this study suggest that binocular rivalry rate may be more associated with the "negative" symptoms of psychosis related to arousal and attentional dysfunction than with the "positive" symptoms of these conditions. Interestingly, some visual deficits such as reduced contrast sensitivity and increased visual backward masking also have been linked to negative rather than positive symptoms of schizophrenia (Cimmer et al. 2006; Slaghuis 2004). Therefore, further comparison of the visual deficits induced by psilocybin and those observed in clinical populations may help uncover the pharmacological processes underlying these symptom-specific effects.

Selective blockade of the 5-HT_{2A} receptor had no measurable influence on psilocybin's slowing of binocular rivalry rate, suggesting a possible involvement of other receptors. One of the most obvious candidates is the 5-HT_{1A} receptor. Although it is possible that the 5-HT_{2C} receptor is also involved (Blair et al. 2000), virtually nothing is known of the role of this receptor in the effects of psilocybin or any other hallucinogen. In contrast, the 5-HT_{1A} receptor was recently found to mediate some of the effects of another serotonergic hallucinogen, 5-MeO-DMT (Krebs-Thomson et al. 2006), and this receptor is known to be activated by psilocin, the active metabolite of psilocybin (Blair et al. 2000; McKenna et al. 1990). Although the lack of involvement of the 5-HT_{2A} receptor does not prove a direct contribution of the 5-HT_{1A} receptor, this possibility is consistent with predictions made about the role of the raphe nuclei and other brainstem structures in rivalry switching (Pettigrew 2001). Before any firm conclusions can be drawn, however, the involvement of the 5-HT_{1A} receptor must be tested directly with a selective agonist/antagonist. Of course, even if future research can demonstrate a direct role of the 5-HT_{1A} receptor it will be important to determine whether the relevant factor is the timing of raphe activity, the reduction in 5-HT released into the cortex, or the result of any number of different downstream processes associated with other neurotransmitter systems or intercellular processes. Although we believe that the 5-HT_{1A} receptor is one of the most likely candidates in the effects shown here, there is no expectation of exclusive involvement of this receptor in the slowing of binocular rivalry switch rate. To the contrary, our main claim is that the binocular rivalry switch rate appears to be linked to levels of arousal and attentional function. Therefore, rivalry rate should be sensitive to any pharmacological compounds, which selectively influence these factors. For example, the anti-glutamatergic hallucinogen (S)-ketamine was recently found to be associated with greater "negative" psychosis-like symptoms, whereas the 5-HT_{2A} hallucinogen DMT was found to be associated with relatively greater "positive" psychosis-like effects (Gouzoulis-Mayfrank et al. 2005). On the basis of this finding, we would predict that (S)-ketamine may result in even greater slowing of binocular rivalry switch rate than that caused by equivalent doses of psilocybin or DMT.

One obvious concern with the apparent association between reduced rivalry rate and reductions in arousal and vigilance is the possibility that any inappropriate button response or substantial reduction in reaction time may impair performance and result in "missed" switches. This seems unlikely, however, given that subjects showed no increase in the percentage of incorrect responses during the pretest "catch trial movie" and only a minor increase (0.18 s) in response time compared to placebo at only 1 of the 11 testing times under the psilocybin condition. Furthermore, in addition to the changes in rivalry switch rate, there were also qualitative differences reported, with an increase in the proportion of time subjects experienced the mixed/transitional state of "cross-hatch" or "patchwork" rivalry. This finding is unlikely to result from a general slowing of response times. Rather, it appears that the entire switching process was affected by psilocybin, with a prolongation of both the periods of exclusive dominance and the periods of transition. Together with recent psychophysical evidence highlighting a clear role of attention in binocular rivalry (Chong et al. 2005; Mitchell et al. 2004; Paffen et al. 2006), these results suggest that future studies combining both pharmacological and psychological manipulations of attention may provide some much needed insight into the neural mechanisms by which attention can influence conscious perception.

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